#### What is Claimed:

1. An aldehyde having the formula:

$$\begin{matrix} O & & O \\ \parallel \\ HC(CH_2)_wX\text{-}C\text{-}(Y)_m(CH_2)_z\text{-}O\text{-}PAG\text{-}O(CH_2)_z(Y)_m\text{-}C\text{-}X(CH_2)_wCH \\ \parallel & & \parallel \\ O & & O \end{matrix}$$

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wherein X and Y are individually selected from -O - or - NH- with the proviso that X is NH when m is 1 and Y is - O-, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from about 500 to about 100,000 Daltons, z is an integer of from 2 to 4, m is an integer of from 0 to 1, and w is an integer of from 2 to 8, wherein the aldehyde group is free or protected with a hydrolyzable aldehyde protecting group.

- 2. The aldehyde of claim 1 wherein said residue is formed from polyethylene glycol.
  - 3. The aldehyde of claim 2 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.
  - 4. The aldehyde of claim 1 wherein said aldehyde has a formula:

$$\begin{array}{c} O \\ \parallel \\ HC(CH_2)_wHN\text{-}C\text{-}(CH_2)_z\text{-}O\text{-}PAG\text{-}O(CH_2)_z\text{-}C\text{-}NH(CH_2)_wCH} \\ \parallel \\ O \\ \end{array}$$

wherein PAG, z, and w are as above.

- 5. The aldehyde of claim 4 wherein said divalent residue is polyethylene glycol.
- 6. The aldehyde of claim 5 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.
- 5 7. The aldehyde of claim 5 wherein the molecular weight of the residue is about 10,000 Daltons.
  - 8. The aldehyde of claim 5 wherein the molecular weight of the residue is about 20,000 Daltons.
  - 9. The aldehyde of claim 1 wherein said aldehyde has a formula:

$$\begin{array}{c} O \\ \parallel \\ HC(CH_2)_wHN\text{-}C\text{-}O(CH_2)_z\text{-}O\text{-}PAG\text{-}O(CH_2)_zO\text{-}C\text{-}NH(CH_2)_wCH} \\ \parallel \\ O \end{array}$$

IA-2

wherein PAG, z and w are as above.

- 10. The aldehyde of claim 9 wherein said divalent residue is formed from polyethylene glycol.
- 15 11. The aldehyde of claim 10 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.
  - 12. The aldehyde of claim 10 wherein the said residue has a molecular weight of 20,000 Daltons.
  - 13. The aldehyde of claim 1 having the formula:

$$\begin{matrix} \mathbf{O} & \mathbf{O} \\ \parallel & \parallel \\ \mathbf{OHC(CH_2)_w\text{-}HN\text{-}C\text{-}HN(CH_2)_zO\text{-}PAG\text{-}O(CH_2)_zNH\text{-}C\text{-}NH\text{-}(CH_2)_wCHO} \end{matrix}$$

IA-3

wherein PAG, z and w are as above.

- 14. The compound of claim 13 wherein said divalent residue is polyethylene glycol.
- 5 15. The compound of claim 14 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.
  - 16. The aldehyde of claim 14 wherein the molecular weight of the residue is 20,000 Daltons.
  - 17. The aldehyde of claim 1 having the formula:

 $\begin{array}{c} O & O \\ \parallel & \parallel \\ OHC(CH_2)_w \text{-O-C-HN}(CH_2)_z O\text{-PAG-O}(CH_2)_z NH\text{-C-O-}(CH_2)_w CHO \end{array}$ 

IA-4

wherein PAG, z and w are as above.

- 15 18. The aldehyde of claim 17 wherein said divalent residue is formed from polyethylene glycol.
  - 19. The compound of claim 18 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.
  - 20. The aldehyde of claim 18 wherein the molecular weight of the residue is 20,000 Daltons.
    - 21. An aldehyde of the formula:

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wherein R is hydrogen or lower alkyl, w is an integer from 2 to 8, y is an integer of from 2 to 4, and PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from about 500 to about 100,000 Daltons.

- 22. The aldehyde of claim 21 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000 Daltons.
  - 23. The aldehyde of claim 22 where R is methyl and the PEG residue has a molecular weight of about 10,000 Daltons.
  - 24. The aldehyde of claim 22 wherein R is methyl and the PEG residue has a molecular weight of 20,000 Daltons.
- 15 25. An aldehyde of the formula:

$$\begin{array}{c}
O & O \\
O & W \\
N(CH_2)_zO\text{-PAG-O(CH_2)}_z(Y)_m\text{-C-X(CH_2)}_wCH
\end{array}$$

ID

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wherein X and Y are individually selected from -O - or - NH- with the proviso that X is NH when m is 1 and Y is -O-, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, z is an integer of from 2 to 4, m is an integer of from 0 to 1, and w is an integer of from 2 to 8.

- 26. The aldehyde of claim 25 wherein said residue is formed from polyethylene glycol.
  - 27. The aldehyde of claim 26 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.
  - 28. The aldehyde of claim 25 wherein said aldehyde has a formula:

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wherein PAG, z and w are as above.

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- 29. The aldehyde of claim 28 wherein said divalent residue is polyethylene glycol.
- 30. The aldehyde of claim 29 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.

- 31. The aldehyde of claim 29 wherein the molecular weight of the residue is about 10,000 Daltons.
- 32. The aldehyde of claim 29 wherein the molecular weight of the residue is about 20,000 Daltons.
- 5 33. The aldehyde of claim 25 wherein said aldehyde has a formula:

ID-2

wherein PAG, z and w are as above.

- 34. The aldehyde of claim 33 wherein said divalent residue is polyethylene glycol.
- 35. The aldehyde of claim 34 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.
- 15 36. The aldehyde of claim 34 wherein the molecular weight of the residue is about 10,000 Daltons.
  - 37. The aldehyde of claim 34 wherein the molecular weight of the residue is about 20,000 Daltons.
  - 38. An aldehyde of the formula:

wherein X and Y are individually selected from -O - or - NH- with the proviso that X is NH when m is 1 and Y is - O-, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, z is an integer of from 2 to 4, m is an integer of from 0 to 1, p is an integer of from 1 to 10, and w is an integer of from 2 to 8.

10 39. The aldehyde of claim 38 wherein said aldehyde has a formula:

$$O O O O O$$

$$\parallel N(CH_2)_p-C-NH(CH_2)_zO-PAG-O(CH_2)_z-C-NH(CH_2)_wCH$$

E-1

wherein PAG, p, z and w are as above.

- 15 40. The aldehyde of claim 39 wherein said divalent residue is polyethylene glycol.
  - 41. The aldehyde of claim 40 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.
  - 42. The aldehyde of claim 40 wherein the molecular weight of the residue is about 10,000 Daltons.
- 20 43. The aldehyde of claim 40 wherein the molecular weight of the residue is about 20,000 Daltons.

44. The aldehyde of claim 38 wherein said aldehyde has a formula:

IE-2

wherein PAG, p, z and w are as above.

- 45. The aldehyde of claim 44 wherein said divalent residue is polyethylene glycol.
- 5 46. The aldehyde of claim 45 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.
  - 47. The aldehyde of claim 45 wherein the molecular weight of the residue is about 10,000 Daltons.
- 48. The aldehyde of claim 45 wherein the molecular weight of the residue is about 20,000 Daltons.
  - 49. A homobifunctional N-maleimidyl polymer of the formula:

$$\begin{array}{c|c}
O & O & O \\
N(CH_2)_p - C - NH(CH_2)_z - O - PAG - O - (CH_2)_z NH - C - (CH_2)_p N
\end{array}$$

IG

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wherein PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and

having a molecular weight of from about 500 to about 100,000 Daltons, p is an integer of from 1 to 10, and z is an integer of from 2 to 4.

- 50. The compound of claim 49 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000 Daltons.
  - 51. An aldehyde of the formula:

$$\begin{array}{c} \text{H} & \text{O} \\ \text{O} & (\text{CH}_2)_w \\ \text{RO-PAG-O(CH}_2)_z\text{-O-C-NH-CH-COOH} \end{array}$$

wherein PAG,R, w and z are as above.

- 52. The aldehyde of claim 51 wherein said residue is formed from polyethylene glycol
- 53. The aldehyde of claim 52 wherein the residue has a molecular weight of 5,000 to 50,000 Daltons.
  - 54. The amino acid of the formula:

$$\begin{array}{c} HO \\ HO \\ R_{13} \\ (CH_2)_w \\ OH \\ C \\ O \end{array}$$

55.

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56. wherein  $R_{13}$  is hydrogen alkyl, or phenyl and w is an integer of from 2 to 8.

55. The amino acid of the formula:

$$\begin{array}{c|c}
F_1 & F \\
\hline
 & R_{13} \\
\hline
 & C \\
\hline
 & OH \\
\hline
 & OH
\end{array}$$

wherein  $F_1$  and F are individually selected from -OH or  $-NH_2$  with the proviso that  $F_1$  is  $-NH_2$  when F is -OH and  $F_1$  is -OH when F is  $-NH_2$ .  $R_{13}$  and W are as above.

56. A compound of the formula:

$$\begin{matrix} R^1(CH_2)_wX\text{-}C\text{-}(Y)_m(CH_2)_z\text{-}O\text{-}PAG\text{-}O(CH_2)_z(Y)_m\text{-}C\text{-}X(CH_2)_wR^1 \\ 0 \end{matrix}$$

wherein R¹ is CH(OH)CH(OH)R² and wherein R² is selected from a group consisting of hydrogen, alkyl, or phenyl, X and Y are individually selected from -O- or - NH- with the proviso that X is NH when m is 1 and Y is-O-, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from about 500 to about 100,000 Daltons, z is an integer of from 2 to 4, m is an integer of from 0 to 1; and w is an integer of from 2 to 8.

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### 57. A compound of the formula:

$$\begin{array}{c} O \\ \parallel \\ NH\text{-}C\text{-}O\text{-}(CH_2)_w\text{-}R^1 \\ (CH_2)_y \\ \parallel \\ CH_2)_w\text{-}O\text{-}C\text{-}NH\text{-}CH\text{-}C\text{-}NH\text{-}PAGOR} \\ \parallel \\ O \end{array}$$

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wherein R is hydrogen or alkyl, R¹ is -CH(OH)CH(OH)R² and wherein R² is selected from a group consisting of hydrogen, alkyl, or phenyl, w is an integer from 2 to 8, y is an integer of from 2 to 4, and PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from about 500 to about 100,000 Daltons.

### 58. A compound of the formula:

$$R^{1}$$
- $(CH_{2})_{w}$ -O- $(CH_{2})_{z}$ O-PAG-O $(CH_{2})_{z}$ -O- $(CH_{2})_{w}$ - $R^{1}$ 

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wherein R<sup>1</sup> is CH(OH)CH(OH)R<sup>2</sup> and wherein R<sup>2</sup> is selected from a group consisting of hydrogen, alkyl, or phenyl, w is an integer from 3 to 8, z is an integer of from 2 to 4, and PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a

molecular weight of from about 500 to about 100,000 Daltons.

## 59. A compound of the formula:

$$\begin{array}{c}
O \\
O \\
N(CH_2)_zO-PAG-O(CH_2)_z(Y)_m-C-X(CH_2)_wR^1
\end{array}$$

wherein wherein R¹ is CH(OH)CH(OH)R² and wherein R² is selected from a group consisting of hydrogen, alkyl, or phenyl, X and Y are individually selected from -O - or - NH- with the proviso that X is NH when m is 1 and Y is - O-, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, z is an integer of from 2 to 4, m is an integer of from 0 to 1, and w is an integer of from 2 to 8.

## 60. A compound of the formula:

$$O \\ | \\ N(CH_2)_p-C-NH(CH_2)_z-O-PAG-O-(CH_2)_z(Y)_m-C-X(CH_2)_wR^1$$

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wherein R¹ is CH(OH)CH(OH)R² and wherein R² is selected from a group consisting of hydrogen, alkyl, or phenyl, X and Y are individually selected from -O - or - NH- with the proviso that X is NH when m is 1 and Y is -O-, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, z is an integer of from 2 to 4, m is an integer of from 0 to 1, p is an integer of from 1 to 10, and w is an integer of from 2 to 8.

### 10 61. A compound of the formula:

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$$CH_2 = CH - S - (CH_2)_z O - PAG - O - (CH_2)_z C NH(CH)_w R^1$$

$$0$$

wherein R¹ is CH(OH)CH(OH)R² and wherein R² is selected from a group consisting of hydrogen, alkyl, or phenyl, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, z is an integer of from 2 to 4, and w is an integer of from 2 to 8.

# 20 62. A conjugate of the formula:

$$\begin{array}{c} P_1HNCH_2(CH_2)_wX\text{-}C\text{-}(Y)_m(CH_2)_z\text{-}O\text{-}PAG\text{-}O(CH_2)_z(Y)_m\text{-}C\text{-}X(CH_2)_wCH_2NHP_1\\ \\ O \\ \end{array}$$

wherein P<sub>1</sub> is a protein residue with its amino group removed, X and Y are individually selected from -O- or -NH with the proviso that X is NH when m is 1 and Y is -O-, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, z is an integer of from 2 to 4, m is an integer of from 0 to 1, and w is an integer of from 2 to 8.

10 63. The conjugate of claim 62 where said conjugate has the formula:

$$O \\ \parallel \\ P_1 HNCH_2 (CH_2)_w HN-C-(CH_2)_z -O-PAG-O(CH_2)_z -C-NH(CH_2)_w CH_2 NHP_1$$

IIA-1

wherein  $P_1$ , PAG, w and z are as above.

- 64. The conjugate of claim 63 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000.
- 65. The conjugate of claim 64 where said P<sub>1</sub> can be G-CSF, EPO, IFN-•, IFN-• or Hemoglobin.
  - 66. The conjugate of claim 63 where said conjugate has the formula:

$$\begin{matrix} O & O \\ \parallel & \parallel \\ P_1 HNCH_2(CH_2)_w HN-C-O(CH_2)_z -O-PAG-O(CH_2)_z O-C-NH(CH_2)_w CH_2NHP_1 \end{matrix}$$

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wherein  $P_1$ , PAG, w and z are as above.

- 67. The conjugate of claim 66 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000.
- 68. The conjugate of claim 67 where said  $P_1$  can be G-CSF, EPO, IFN-•, IFN-• or Hemoglobin.
- 69. The conjugate of claim 62 where said conjugate has the formula:

$$\begin{matrix} \mathbf{O} & \mathbf{O} \\ \parallel & \parallel \\ \mathbf{P_1HNCH_2(CH_2)_wHN-C-NH(CH_2)_z-O-PAG-O(CH_2)_zHN-C-NH(CH_2)_wCH_2NHP_1} \end{matrix}$$

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IIA-3

wherein P<sub>1</sub>, PAG, w and z are as above,

- 70. The conjugate of claim 69 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000.
- 71. The conjugate of claim 70 where  $P_1$  can be G-CSF, EPO, IFN-•, IFN-• or Hemoglobin.
- 72. The conjugate of claim 62 where said conjugate has the formula:

$$\begin{matrix} O & O \\ \parallel & \parallel \\ P_1 HNCH_2 (CH_2)_w O-C-NH(CH_2)_z -O-PAG-O(CH_2)_z HN-C-O(CH_2)_w CH_2 NHP_1 \end{matrix}$$

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IIA-4

wherein P<sub>1</sub>, PAG, w and z are as above.

- 73. The conjugate of claim 72 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000.
- 74. The conjugate of claim 73 where said  $P_1$  can be G-CSF, EPO, IFN-•, IFN-• or Hemoglobin.
- 5 75. A conjugate of the formula:

$$\begin{array}{c|c} HN & & & & & \\ \hline & P_{\overline{3}} & & & & \\ \hline & O & & & & \\ \hline & O & & & & \\ \hline & CH_2(CH_2)_wX-C-(Y)_m(CH_2)_z-O-PAG^1-O(CH_2)_z(Y)_m-C-X(CH_2)_wCH_2 \end{array}$$

**IIAA** 

wherein [P<sub>3</sub>] is the divalent residue of a protein resulting from removal of two of its primary amino groups, X and Y are individually selected from -O- or -NH with the proviso that X is NH when m is 1 and Y is -O-, PAG¹ is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 20,000 Daltons, z is an integer of from 2 to 4, m is an integer of from 0 to 1, and w is an integer of from 2 to 8.

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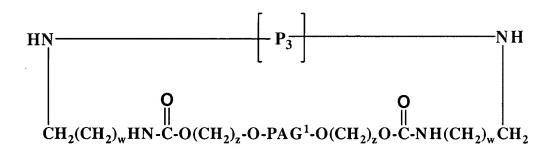
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76. The conjugate of claim 75 were said conjugate has the formula:

$$\begin{array}{c|c} HN & & & & \\ \hline & Q & & & \\ \hline & O & & & \\ \hline & CH_2(CH_2)_wHN\text{-}C\text{-}(CH_2)_z\text{-}O\text{-}PAG^1\text{-}O(CH_2)_z\text{-}C\text{-}NH(CH_2)_wCH_2} \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ &$$

wherein  $[P_3]$ ,  $PAG^1$ , w and z are as above.

- 77. The conjugate of claim 76 wherein PAG is formed from polyethylene glycol having a molecular weight of from 500 to 5,000
- 78. The conjugate of claim 77 where said  $[P_3]$  is Hemoglobin.
- 79. The conjugate of claim 75 where said conjugate has the formula:



IIAA-2

wherein [P<sub>3</sub>], PAG<sup>1</sup>, w and z are as above.

- 80. The conjugate of claim 79 wherein PAG is formed from polyethylene glycol having a molecular weight of from 500 to 5,000.
- 81. The conjugate of claim 80 where said  $[P_3]$  is G-CSF, EPO, IFN-•, IFN-• or Hemoglobin.

82. The conjugate of claim 75 where said conjugate has the formula:

$$\begin{array}{c|c} & & & & \\ & &$$

IIAA-3

wherein  $[P_3]$ , PAG<sup>1</sup>, w and z are as above.

- 5 83. The conjugate of claim 82 wherein PAG is formed from polyethylene glycol having a molecular weight of from 500 to 5,000.
  - 84. The conjugate of claim 83 where said  $[P_3]$  is Hemoglobin.
  - 85. The conjugate of claim 75 where said conjugate has the formula:

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IIAA-4

wherein  $[P_3]$ , PAG<sup>1</sup>, w and z are as above.

- 86. The conjugate of claim 85 wherein PAG is formed from polyethylene glycol having a molecular weight of from 500 to 5,000.
- 87. The conjugate of claim 86 where said  $[P_3]$  is Hemoglobin.

88. A conjugate of the formula:

$$\begin{array}{c} O \\ \parallel \\ NH\text{-}C\text{-}O\text{-}(CH_2)_w\text{-}CH_2NHP_1 \\ (CH_2)_y \\ \downarrow \\ P_1HNCH_2\text{-}(CH_2)_w\text{-}O\text{-}C\text{-}NH\text{-}CH\text{-}C\text{-}NH\text{-}PAGOR \\ \parallel & \parallel \\ O & O \end{array}$$

IIB

wherein P<sub>1</sub> is a protein residue with its amino group removed, PAG is a divalent residue of poly lower alkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, R is hydrogen or lower alkyl, w is an integer of from 2 to 8, and y is an integer of from 2 to 4.

- 10 89. The conjugate of claim 88 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000.
  - 90. The conjugate of claim 89 where said P<sub>1</sub> may be G-CSF, EPO, IFN-•, IFN-• or hemoglobin.
  - 91. A conjugate of the formula:

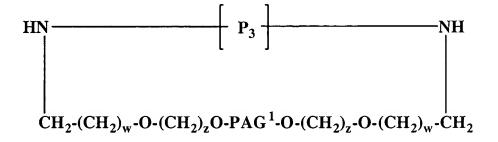
**IIBB** 

wherein [P<sub>3</sub>] is the divalent residue of a protein resulting from removal of two of its primary amino groups, R is hydrogen or lower alkyl, PAG is a divalent residue of poly lower alkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, w is an integer of from 2 to 8, and y is an integer of from 2 to 4.

- 10 92. The conjugate of claim 91 wherein PAG is formed from polyethylene glycol having a molecular weight of from 500 to 5,000.
  - 93. The conjugate of claim 92 where said [P<sub>3</sub>] is Hemoglobin.
  - 94. The conjugate of claim 93 wherein PAG is formed from polyethylene glycol having a molecular weight of from 500 to 10,000.
- 15 95. A conjugate of the formula:

wherein  $P_1$  is a protein residue with its amino group removed, PAG is a divalent residue of poly lower alkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, w is an integer of from 2 to 8, and z is an integer of from 2 to 4.

- 96. The conjugate of claim 95 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000.
  - 97. A conjugate of the formula:



**IICC** 

wherein [P<sub>3</sub>] is the divalent residue of a protein resulting from removal of two of its primary amino groups, PAG¹ is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a

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molecular weight of from 500 to 20,000 Daltons, z is an integer of from 2 to 4, and w is an integer of from 2 to 8.

- 98. The conjugate of claim 97 wherein PAG is formed from polyethylene glycol having a molecular weight of from 500 to 5,000.
- 5 99. The conjugate of claim 98 where said  $[P_3]$  is Hemoglobin.
  - 100. A conjugate of the formula:

$$P_{2} \xrightarrow{O} \\ N(CH_{2})_{z}O-PAG-O(CH_{2})_{z}(Y)_{m}-C-X(CH_{2})_{w}CH_{2}NHP_{1}$$

IID

wherein  $P_2$  is a residue of a protein having its sulfhydryl group removed,  $P_1$  is a residue of a protein having its amino group removed, X and Y are individually selected from -O or -NH- with the proviso that X is NH when m is 1 and Y is -O-, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, z is an integer of from 2 to 4, m is an integer of from 0 to 1, and w is an integer of from 2 to 8.

101. The conjugate of claim 100 where said conjugate has the formula:

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$$P_{2} \xrightarrow{\mathbf{O}} \mathbf{N}(\mathbf{CH}_{2})_{\mathbf{z}}\mathbf{O}\text{-PAG-O}(\mathbf{CH}_{2})_{\mathbf{z}}\text{-C-NH}(\mathbf{CH}_{2})_{\mathbf{w}}\mathbf{CH}_{2}\mathbf{NHP}_{1}$$

IID-1

wherein  $P_1$ ,  $P_2$  PAG, z and w are as above.

- 102. The conjugate of claim 101 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000.
- 5 103. The conjugate of claim 100 where said conjugate has the formula:

$$P_{2} \xrightarrow{\mathbf{O}} \mathbf{N}(\mathbf{CH}_{2})_{\mathbf{z}}\mathbf{O}\text{-PAG-O}(\mathbf{CH}_{2})_{\mathbf{z}}\mathbf{O}\text{-C-NH}(\mathbf{CH}_{2})_{\mathbf{w}}\mathbf{CH}_{2}\mathbf{NHP}_{1}$$

IID-2

wherein  $P_{1}$ ,  $P_{2}$ , PAG, z and w are as above.

10 104. The conjugate of claim 103 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000.

### 105. The conjugate of the formula:

$$\begin{array}{c|c} & & & \\ & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\$$

IIDD

wherein  $[P_4]$  is the divalent residue of a protein resulting from removal of a primary amino group and a sulfhydryl group, X and Y are individually selected from -O - or - NH-with the proviso that X is NH when m is 1 and Y is -O-,  $PAG^1$  is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 20,000 Daltons, z is an integer of from 2 to 4, m is an integer of from 0 to 1, and w is an integer of from 2 to 8.

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- 106. The conjugate of claim 105 wherein PAG is formed from polyethylene glycol having a molecular weight of from 500 to 5,000.
- 107. The conjugate of claim 106 where said  $[P_4]$  is Hemoglobin.

108. The conjugate of the formula:

$$P_{2} \xrightarrow{S} \begin{array}{c} O \\ O \\ \parallel \\ N(CH_{2})_{p}\text{-C-NH}(CH_{2})_{z}O\text{-PAG-O}(CH_{2})_{z}(Y)_{m}\text{-C-X}(CH_{2})_{w}CH_{2}NHP_{1} \end{array}$$

$$IIE$$

wherein  $P_2$  is a residue of a protein having its sulfhydryl group removed,  $P_1$  is a residue of a protein having its amino

group removed, X and Y are individually selected from -O -

or - NH- with the proviso that X is NH when m is 1 and Y is

-O-, PAG is a divalent residue of polyalkylene glycol

resulting from removal of the terminal hydroxy groups and

having a molecular weight of from 500 to 100,000 Daltons, p

is an integer of from 1 to 10, z is an integer of from 2 to 4, m

is an integer of from 0 to 1, and w is an integer of from 2 to 8.

109. The conjugate of claim 108 where said conjugate has the formula:

IIE-1

wherein P<sub>1</sub>, P<sub>2</sub> PAG, p, z and w are as above.

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- 110. The conjugate of claim 109 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000
- 111. The conjugate of claim 108 where said conjugate has the formula:

$$P_{2} \xrightarrow{S} \begin{array}{c} O \\ O \\ \parallel \\ N(CH_{2})_{p}\text{-C-NH}(CH_{2})_{z}O\text{-PAG-O}(CH_{2})_{z}O\text{-C-NH}(CH_{2})_{w}CH_{2}NHP_{1} \\ O \\ IIE-2 \end{array}$$

wherein P<sub>1</sub>, P<sub>2</sub> PAG, p, z and w are as above.

- 112. The conjugate of claim 111 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000.
- 113. The conjugate of the formula:

$$\begin{array}{c|c} & & & & \\ & &$$

wherein  $[P_4]$  is the divalent residue of a protein resulting from removal of a primary amino group and a sulfhydryl group, X and Y are individually selected from -O - or - NH-

10

with the proviso that X is NH when m is 1 and Y is –O-, PAG¹ is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 20,000 Daltons, p is an integer of from 1 to 10, m is an integer of from 0 to 1, and w is an integer of from 2 to 8.

- 114. The conjugate of claim 113 wherein PAG is formed from polyethylene glycol having a molecular weight of from 500 to 5,000.
- 115. The conjugate of claim 114 where said  $[P_4]$  is Hemoglobin.
- 10 116. A conjugate of the formula:

5

$$\begin{array}{c} O & O \\ \parallel & \parallel \\ P_2S\text{-}CH_2CH_2\text{-}S\text{-}(CH_2)_zO\text{-}PAG\text{-}O(CH_2)_zCNH(CH_2)_wCH_2NHP_1 \\ \parallel & O \end{array}$$

IIF

wherein  $P_2$  is a residue of a protein having its sulfhydryl group removed,  $P_1$  is a residue of a protein having its amino group removed, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, z is an integer of from 2 to 4, and w is an integer of from 2 to 8.

20 117. The conjugate of claim 116 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000.

### 118. A conjugate of the formula:

**IIFF** 

wherein [P<sub>4</sub>] is the divalent residue of a protein resulting from removal of a primary amino group and a sulfhydryl group, PAG<sup>1</sup> is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 20,000 Daltons, z is an integer of from 2 to 4, and w is an integer of from 2 to 8.

- 119. The conjugate of claim 118 wherein PAG is formed from polyethylene glycol having a molecular weight of from 500 to 5,000.
- 120. The conjugate of claim 119 where said  $[P_4]$  is Hemoglobin.
- 121. A conjugate of the formula:

$$P_{2} \xrightarrow{S} \begin{array}{c} O \\ O \\ N(CH_{2})_{p}\text{-}C\text{-}NH(CH_{2})_{z}\text{-}O\text{-}PAG\text{-}O\text{-}(CH_{2})_{z}NH\text{-}C\text{-}(CH_{2})_{p}N} \\ O \end{array}$$

5

wherein  $P_2$  is a residue of a protein resulting from removal of a sulfhydryl group, PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, p is an integer of from 1 to 10, and z is an integer of from 2 to 4.

- 122. The conjugate of claim 121 wherein PAG is formed from polyethylene glycol having a molecular weight of from 5,000 to 50,000.
- 123. The conjugate of claim 121 wherein the residue has a molecular weight of 500 to 5,000 Daltons.
  - 124. The conjugate of the formula:

$$\begin{array}{c|c} & & & & \\ &$$

**IIGG** 

wherein [P<sub>5</sub>] is the divalent residue of a protein resulting from removal of two sulfhydryl groups, PAG¹ is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of

15

from 500 to 20,000 Daltons, p is an integer of from 1 to 10, and z is an integer of from 2 to 4.

- 125. The conjugate of claim 124 wherein PAG is formed from polyethylene glycol having a molecular weight of from 500 to 5,000.
- 5 126. The conjugate of claim 125 where said [P<sub>5</sub>] is Hemoglobin.
  - 127. A process for producing an aldehyde of the formula:

$$\begin{matrix} \mathbf{O} & \mathbf{O} \\ \parallel \\ \mathbf{HC\text{-}(CH_2)_w\text{-}O\text{-}(CH_2)_zO\text{-}PAG\text{-}O(CH_2)_z\text{-}O\text{-}(CH_2)_w\text{-}CH} \end{matrix}$$

wherein PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, z is an integer of from 2 to 4, and w is an integer of from 2 to 8;

wherein PAG and z are as above;

15 comprising halogenating said hydroxy compound to form a halide of the formula

$$X-(CH_2)_z$$
-O-PAG-O- $(CH_2)_z$ - $X$ 

by reacting said hydroxy compound with a halogenating agent having the formula

wherein X is a halogen;

from a hydroxy compound of the formula

to form said halide, and reacting said halide with an alkoxide of the formula

$$BO$$
 $(CH_2)_w$ 
 $R_{13}$ 

wherein  $R_{13}$  is hydrogen, alkyl or phenyl,w is as above and B is an alkali metal salt;

5 to form a polymeric acetonide of the formula

wherein PAG,  $R_{13}$ , and z are as above, and w is an integer of

from 2 to 8

and thereafter hydrolyzing said polymeric acetonide under acid conditions to remove the acetonide group, and thereafter subjecting said hydrolyzed acetonide to oxidation with a periodate oxidizing agent to form said dialdehyde.

128. A process for producing an aldehyde of the formula

$$\begin{matrix} \mathbf{O} & \mathbf{O} \\ \parallel & \parallel \\ \mathbf{HC\text{-}(CH_2)_w\text{-}O\text{-}(CH_2)_zO\text{-}PAG\text{-}O(CH_2)_z\text{-}O\text{-}(CH_2)_w\text{-}CH} \end{matrix}$$

wherein PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, z is an integer of from 2 to 4, and w is an integer of from 2 to 8; from a hydroxy compound of the formula

wherein PAG and z are as above;

comprising esterifying said hydroxy compound to form an ester of the formula

wherein PAG and z are as above and OL is a sulfonate leaving group;

by reacting said hydroxy compound with a sulfonating agent having the formula

15 HaloL

wherein L is a sulfonyl leaving group and Halo is a halogen; to form said sulfonate ester, and reacting said ester with an alkoxide of the formula

5

wherein  $R_{13}$ , andw are as above and B is an alkali metal salt; to form a polymeric acetonide of the formula

wherein PAG, R<sub>13</sub>, z and w are as above;

and thereafter hydrolyzing said polymeric acetonide under acid conditions to remove the acetonide group, and thereafter subjecting said hydrolyzed acetonide to oxidation with a periodate oxidizing agent to form said aldehyde.

129. A process for producing an aldehyde of the formula:

$$CH_2=CH-S-(CH_2)_zO-PAG-O(CH_2)_zCNH(CH_2)_wCH$$

10

5

wherein PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, and w is an integer of from 2 to 8;

15 from a vinyl sulfone of the formula

$$CH_2 = CH - S - (CH_2)_z O - PAG - O - (CH_2)_z C - O - N$$

wherein PAG, z and w are as above;

by reacting said sulfone with an amino acetal of the formula

5 wherein R is lower alkyl and w is as above;

to produce the amide derivative of the formula:

$$CH_2=CH-S-(CH_2)_zO-PAG-O-(CH_2)_zC-NH(CH_2)_wCH(OR)_2$$

wherein PAG, R and w are as above;

and thereafter hydrolyzing said polymeric acetal under acid conditions to form said aldehyde.

130. A process for producing an aldehyde of the formula

$$O O O O$$

$$\parallel N(CH_2)_p-C-NH(CH_2)_zO-PAG-O(CH_2)_z-C-NH(CH_2)_wCH$$

wherein PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, z is an integer of from 2 to 4, p is an integer of from 1 to 10, and w is an integer of from 2 to 8;

from an amino-carboxy derivative of the formula

## NH<sub>2</sub>(CH<sub>2</sub>)<sub>p</sub>COOH

wherein p is as above;

by reacting said derivative with maleic anhydride and pentafluorophenyl trifluoroacetate to produce the compound of the formula

$$\begin{array}{c|c}
O & F & F \\
O & \parallel & F \\
\hline
O & F & F
\end{array}$$

$$\begin{array}{c|c}
F & F & F \\
\hline
F & F & F
\end{array}$$

wherein p is as above;

which derivative is conjugated with the compound of the formula

wherein PAG and z are as above;

to form the acid derivative

5

10

$$\begin{array}{c}
O \\
O \\
N(CH_2)_p - C - NH(CH_2)_z O - PAG - O(CH_2)_z - C - OH
\end{array}$$

wherein PAG, p and z are as above;

which compound is converted to an active ester whereby L may represent derivatives such as pentafluoro phenol or N-hydroxysuccinimidyl and which compound is described by the formula:

5

wherein PAG, p and z are as above and L is an active leaving group;

and which compound may be condensed with an acetal such as

10

wherein R is lower alkyl and w is as above;

to form the polymeric derivative

wherein PAG, R, p, w and z are as above;

and thereafter hydrolyzing said polymeric acetal under acid conditions to form said aldehyde.

131. A process for producing an aldehyde of the formula:

$$\begin{array}{c|c}
O & O & O \\
\parallel & \parallel & \parallel \\
N(CH_2)_p - C - NH(CH_2)_z O - PAG - O(CH_2)_z O - C - NH(CH_2)_w CH
\end{array}$$

wherein PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, z is an integer of from 2 to 4, p is an integer of from 1 to 10, and w is an integer of from 2 to 8;

from an amino-acid derivative of the formula

wherein p is as above;

by reacting said derivative with maleic anhydride and pentafluorophenyl trifluoroacetate to produce the compound of the formula

$$\begin{array}{c|c}
O & F & F \\
O & \parallel & \\
N(CH_2)_p - CO & F & F
\end{array}$$

wherein p is as above;

which derivative is conjugated with the compound of the formula

wherein PAG and z are as above;

to form the maleimido-alcohol derivative;

$$O \\ N(CH_2)_p - C - NH(CH_2)_z O - PAG - O(CH_2)_z - OH$$

wherein PAG, p and z are as above;

which compound is converted to an active carbonate wherein L may represent such groups as such as p-nitrophenol or N-hydroxysuccinimidyl;

$$O \\ N(CH_2)_p - C - NH(CH_2)_z O - PAG - O(CH_2)_z - OCOL$$

wherein PAG, p and z are as above and L is an active leaving group;

and which compound may then be condensed with an acetal such as

5

## NH<sub>2</sub>(CH<sub>2</sub>)<sub>w</sub>CH(OR)<sub>2</sub>

wherein R is lower alkyl and w is as above; to form the polymeric derivative

$$O \\ O \\ O \\ N(CH_2)_p-C-NH(CH_2)_zO-PAG-O(CH_2)_zO-C-NH(CH_2)_wCH(OR)_2$$

wherein PAG, R, p, w and z are as above;

and thereafter hydrolyzing said polymeric acetal under acid conditions to form said aldehyde.

132. A process for producing an aldehyde of the formula:

$$O O O O O$$

$$\parallel N(CH_2)_2O-PAG-O(CH_2)_2-C-NH(CH_2)_wCH$$

wherein PAG is a divalent residue of polyalkylene glycol

resulting from removal of the terminal hydroxy groups and

having a molecular weight of from 500 to 100,000 Daltons, z

is an integer of from 2 to 4, and w is an integer of from 2 to 8;

from an amino-carboxy derivative of the formula

wherein PAG and z are as above;

125

by reacting said compound with a mixture of maleic anhydride and pentafluorophenyl trifluoroacetate to form the maleimido ester of the formula

$$\begin{array}{c|c}
O & F & F \\
O & & \\
F & & \\
F & & \\
\end{array}$$

wherein PAG and z are as above;

5 and reacting said ester with the acetal of the formula

wherein R is lower alkyl and w is as above;

to form the polymeric derivative

wherein PAG, R, w and z are as above;

and thereafter hydrolyzing said polymeric acetal under acid conditions to form said aldehyde.

133. A process for producing an aldehyde of the formula:

$$O O O O O$$

$$\parallel CH_2)_z O-PAG-O(CH_2)_z O-C-NH(CH_2)_w CH$$

wherein PAG is a divalent residue of polyalkylene glycol resulting from removal of the terminal hydroxy groups and having a molecular weight of from 500 to 100,000 Daltons, z is an integer of from 2 to 4, and w is an integer of from 2 to 8;

by reacting the amino-carboxy derivative of the formula

$$H_2N(CH_2)_2$$
-O-PAG-O-( $CH_2$ )2OH

wherein PAG and z are as above;

with a mixture of maleic anhydride and pentafluorophenyl trifluoroacetate to form the maleimido alcohol of the formula

wherein PAG and z are as above;

which compound is converted to an active carbonate wherein L may represent such groups as such as p-nitrophenol or N-hydroxysuccinimidyl;

$$O \\ O \\ N(CH_2)_zO-PAG-O(CH_2)_zO-C-L$$

wherein PAG and z are as above and L is an active leaving group;

and which compound may be condensed with an acetal such as

NH<sub>2</sub>(CH<sub>2</sub>)<sub>w</sub>CH(OR)<sub>2</sub>

wherein R is lower alkyl and w is as above;

to form the acetal derivative of formula

wherein PAG, R, w and z are as above;

and thereafter hydrolyzing said polymeric acetal under acid conditions to form said aldehyde.

15